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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,841	01/19/2000	Roy A. Gravel	50004/003004	3640

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/487,841	Gravel et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *May 27, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *May 27, 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *Amended claim 6 requires 4 nucleotide and 3 nucleotide deletions, and new claim 35 recites increased risk of cancer by detecting mutation of MTRR raise new issue that requires further consideration and search.*

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Applicants argue that the claims have been amended to limit the MTRR polymorphysm and the specification provides support for the correlation between said polymorphysoms and disease recited (amendment, p. 5-6). This

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*

Claim(s) objected to: *None*

Claim(s) rejected: *1-3, 5-11, 13, 14, and 21-34*

Claim(s) withdrawn from consideration: *12 and 15-20*

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

DETAILED ACTION

Continued from Advisory Action:

is not found persuasive because of the reasons of record. The specification discloses increased risk for mothers to develop neural tube defects (NTD) with combination of homozygous mutant MTRR genotype having an A/G polymorphism at bp 66, which yields an isoleucine (22I) or a methionine (22M) respectively at amino acid position 22, and low cobalamin; mothers of Down's syndrome babies are more likely to have MTRR polymorphism of A->G at nucleotide position 66 and methylenetetrahydrofolate reductase (MTHFR) polymorphism C->T at nucleotide position 677 than control mothers; and individuals having a MTRR homozygous 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 63, 66, 68). The specification only enables the particular MTRR polymorphism with a particular disease as disclosed. The specification only provides a general statement that mutations in MTRR that decrease MTRR activity are likely to be associated with altered risk for cardiovascular disease, NTD, and cancer but fails to provide enabling disclosure to support the claimed invention. Standard methods to rapidly identify G/A polymorphism are just tools to identify MTRR mutations. The specification fails to provide adequate guidance and evidences for the correlation of any polymorphism or mutation within the MTRR gene other than the polymorphism disclosed in the specification with increased risk of

developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo. Different polymorphism or mutation within a gene could result in dramatic different effect on the function of the gene product and therefore, different correlations with increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease. In addition, the specification of the present application discloses that no increased risk of developing NTD could be correlated to a mother or child having homozygous MTRR 22M polymorphism (specification, bridging p. 57-58) and no correlation of increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease with heterozygous or homozygous MTRR G/A polymorphism at nucleotide position 110, or with heterozygous MTRR 22IM polymorphism has been disclosed. It was unpredictable at the time of the invention whether a polymorphism or a mutation within MTRR gene either heterozygous or homozygous would be correlated to increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease, and one skilled in the art at the time of the invention would not be able to predict whether a test subject would have increased risk of developing said diseases by detecting any heterozygous or homozygous polymorphism or mutation within MTRR gene in a test subject. Thus, the claims remain rejected under 35 U.S.C. 112 first paragraph.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.